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For Appellants

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EXAMINER'S ANSWER

This is in response to appellants' brief on appeal filed 10/26/93.

(1) *Status of claims.*

The statement of the status of claims contained in the brief is correct.

(2) *Status of Amendments After Final.*

The appellants' statement of the status of amendments after final rejection contained in the brief is correct.

(3) *Summary of invention.*

The summary of invention contained in the brief is substantially correct. However, appellants incorrectly **imply** that the various variable domains of immunoglobulins were known to have completely different sequences. Appellants have done so by asserting that the term "variable domain" is used to describe portions of immunoglobulin molecules because such portions are inherently variable. It is submitted that the term "variable domain" is used to describe portions of immunoglobulin molecules because such portions are merely **more** variable than most other immunoglobulin domains (such as the constant domains, which are in fact somewhat variable as well). In fact, there are small portions of immunoglobulins which are known as "hypervariable regions" because they have even more sequence variability than "variable domains." It is the examiner's position that the level of variability of the "variable domain" of immunoglobulins is a factual issue for which Kabat et al. (cited below) provides evidence. Kabat et al. shows that the variable domains of immunoglobulins were not known to have completely different sequences.

It is also noted that appellants have included arguments regarding the novelty and advantages of the instant invention over methods of the prior art in the summary. Such arguments should appear in the Arguments section of the Brief.

(4) *Issues.*

The appellants' statement of the issues in the brief is correct. The examiner will show that claims 33-63 are unpatentable under 35 U.S.C. § 103 over Mullis et al., claims 38-45 and 57-63 are unpatentable under 35 U.S.C. § 103 over Skerra et al. in view of Kabat et al. and

either Mullis et al. or Herzog et al., and claims 34-37 and 46-56 are unpatentable under 35 U.S.C. § 103 over Skerra et al. in view of Kabat et al., Schoemaker et al. and either Mullis et al. or Herzog et al.

(5) *Grouping of claims.*

Appellants' brief includes a statement that claims stand or fall together. The examiner agrees that all of the claims on appeal, 33-63, stand or fall together.

(6) *Claims appealed.*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) *Prior Art of record.*

4,683,195 Mullis et al. July 28, 1987.

4,983,728 Herzog et al. January 8, 1991.

4,978,743 Schoemaker et al. December 18, 1990.

Skerra et al. Science, volume 240, pages 1038-1041, 1988.

Kabat et al. Sequences of Proteins of Immunological Interest, Fourth Edition (United States Department of Health and Human Services), pages 494-525, 1987.

Cited by appellants:

Larrick et al. In Vitro Immunization in Hybridoma Technology (Borrebaeck, Ed., Elsevier Science Publishers, Amsterdam), pages 231-246, 1988.

Mullis et al. teach a generic method of cloning any desired target sequences using forward and back primers to produce copies of DNA which lies between primer hybridization sites. This method, known as PCR, uses substantially the same process steps as the instantly claimed method. Mullis et al. also specifically teach the use of a mixture of degenerate primers in a method of cloning target sequences of unspecified or ambiguous sequence.

Herzog et al. teach a PCR method to amplify and clone DNA segments, including the use of mixed primers to amplify and clone related but different DNA sequences.

Schoemaker et al. teach the expression of heterochain antibodies. Schoemaker et al. also teach the advantages of these heterochain antibodies over either parental homochain antibody.

Skerra et al. teach the cloning and expression of DNA encoding immunoglobulin variable chains in E. coli.

Kabat et al. teach the DNA sequences of DNA encoding the variable regions of the heavy and light immunoglobulin chains.

(8) *New prior art.*

No new prior art has been applied in this examiner's answer.

(9) *Grounds of rejection.*

The following grounds of rejection are applicable to the appealed claims.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Appellants are advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 33-63 are rejected under 35 U.S.C. § 103 as being unpatentable over Mullis et al.

Mullis et al. teach a generic method of cloning any desired target sequences using forward and back primers to produce copies of DNA which lies between primer hybridization sites. This method, known as PCR, uses substantially the same process steps as the instantly claimed method. Mullis et al. also specifically teach (column 8, first full paragraph) the use of a mixture of degenerate primers in a method of cloning target sequences of unspecified or ambiguous sequence. Mullis et al. fail to teach the use of primers which would flank an immunoglobulin variable region. However, one of ordinary skill in the art would have reasonably expected, absent evidence to the contrary, that the instantly claimed primers and target sequences would have been operable in the method of Mullis et al. Such an

expectation arises from the explicit teaching by Mullis et al. that their method is generic. A novel starting material or a novel product does not lend patentability to an otherwise conventional process.

Claims 38-45 and 57-63 are rejected under 35 U.S.C. § 103 as being unpatentable over Skerra et al. in view of Kabat et al. and either Mullis et al. or Herzog et al.

Skerra et al. teach the cloning and expression of DNA encoding immunoglobulin variable chains in E. coli. Skerra et al. fail to teach the use of a mixed set of primers to clone related but different DNA sequences.

Mullis et al. was described supra.

Herzog et al. teach (Example 6, column 17) a PCR method to amplify and clone DNA segments, including the use of mixed primers to amplify and clone related but different DNA sequences.

Kabat et al. teach the DNA sequences of DNA encoding the variable regions of the heavy and light immunoglobulin chains.

Accordingly, it would have been obvious to one of ordinary skill in the art to modify the cloning and expression methods of Skerra et al. by using the mixed primer PCR synthesis of Mullis et al. or Herzog et al. One would have been motivated to do so by the ability of mixed primer PCR to clone a population of related but distinct DNA sequences, as taught by Mullis et al. and Herzog et al. One would also have been motivated to apply such a technique to the cloning of DNA encoding immunoglobulin variable domains by the teaching of Kabat et al. that such immunoglobulin DNA varies in sequence.

Claims 34-37 and 46-56 are rejected under 35 U.S.C. § 103 as being unpatentable over Skerra et al. in view of Kabat et al., Schoemaker et al. and either Mullis et al. or Herzog et al.

Mullis et al., Skerra et al., Herzog et al. and Kabat et al. were described supra and are applied as before.

Schoemaker et al. teach the expression of heterochain antibodies. Schoemaker et al. also teach (column 2, fourth full paragraph) the advantages of these heterochain antibodies over either parental homochain antibody.

Accordingly, it would have been obvious to one of ordinary skill in the art to further modify the method of Skerra et al. by expressing different immunoglobulin chains together, as taught by Schoemaker et al., in order to produce heterochain antibodies. It is also noted that, insofar as the claims read on expression of an entire repertoire of cloned DNA, one would have been motivated to express any and all cloned DNA in order to produce the proteins which they encode, a well known goal of genetic engineering.

(10) *New ground of rejection.*

This Examiner's Answer does not contain any new ground of rejection.

(11) *Response to argument.*

Appellants argue (Brief, pages 7 and 8) that one of ordinary skill in the art would not have believed that the process of Mullis et al. could be applied in the context of cloning an immunoglobulin variable domain repertoire. The examiner disagrees. It appears that

appellants are arguing that the instant invention is unobvious due to the alleged breadth of distinct target sequences which could be cloned with the claimed primers, wherein such breadth was allegedly unexpected. Firstly, appellants are misapplying the concept of what need be reasonably expected by one of ordinary skill in the art in order to establish a prima facie case of obviousness. It is submitted that, at a minimum, the examiner needs to establish only that one of ordinary skill in the art would have reasonably expected that the claimed starting materials would have been operable in the method of the prior art. It is the examiner's position that, given the broad teaching of Mullis et al. and the scientific principle contained therein that the specific sequence of a given primer does not, in general, affect its operability in PCR, one of ordinary skill in the art would have reasonably expected that any primer which hybridizes to a target DNA sequence would be operable in the method of Mullis et al. Secondly, a careful reading of the claims reveals that appellants have not in fact claimed a use of primers which is beyond the teaching of Mullis et al. Appellants claim a PCR method which uses forward and back primers wherein the forward and back primers are specific for (i.e. hybridize to) a sequence at or adjacent to the 3' end of the sense or antisense strand, respectively, of each of the target sequences. It is submitted that this is exactly the same principle and use of primers that is taught generically by Mullis et al. In this regard, it is specifically noted that appellants have not claimed any specific limitation as to which DNA sequences **must** be clonable by their method or those DNA sequences which **must** be excluded. In other words, although appellants claim the use of primers which will result in the cloning of sequences encoding at least a part of an immunoglobulin variable domain, there is no claim to how many (or how few) such sequences must (or may) be so cloned by a given

set of primers nor is their any claim that other sequences which do not encode at least a part of an immunoglobulin variable domain must not be clonable by a given set of primers. Thus, there is not even a claim to the use of primers which appellants allege.

Appellants also argue (Brief, page 9, top) that Mullis et al. teach the use of a mixed set of primers for cloning a single target DNA, not for cloning a plurality of target DNA sequences as appellants allege they claim. Firstly, as noted supra, appellants do not, in fact, claim the cloning of any definite number of target sequences. Secondly, it is submitted that one of ordinary skill in the art would have known, based on logical principles, that if a primer set could hybridize to more than one target sequence in a reaction mixture, then more than one target sequence would be amplified and cloned. Finally, it is submitted that Mullis et al. clearly teach that a mixed pool of primers will be operable in their PCR method, which is all that need be shown to establish a prima facie case of non-obviousness.

Appellants assert (Brief, page 10) that Mullis et al. teach that some sequence information is required for each sequence to be amplified. The examiner agrees. However, as quoted by appellants, Mullis et al. state that "[i]t is only necessary that a sufficient number of bases at both ends of the sequence be known **in sufficient detail** so that two oligonucleotides can be prepared which will hybridize to different strands of the desired sequence..." [emphasis added]. It is submitted that the teaching by Mullis et al. that a mixed set of primers based on an amino acid sequence can be used in PCR indicates how little sequence information Mullis et al. considers to be needed to provide sufficient detail such that operable primers can be prepared. It is the examiner's position that Kabat et al. provides

sufficient detail of the instantly targeted DNA sequences encoding immunoglobulin variable domains to prepare operable primers.

The examiner agrees that Skerra et al. does not teach or suggest cloning a repertoire of immunoglobulin variable domain sequences in a single PCR (see Brief, page 10). However, as noted supra, appellants have not claimed any specific number of immunoglobulin variable domain sequences to be cloned in a single PCR. Even if appellants were making such claims, it is submitted that the teachings of Mullis et al. or Herzog et al. supply this missing element.

It is submitted that the instantly claimed method, insofar as it reads on cloning multiple target DNAs of distinct sequence, makes use of primers in the same way that Herzog et al. (and Mullis et al.) do. Specifically, primers which match a given target sequence will amplify that target sequence. The use of multiple primers in Herzog et al. is directed toward cloning multiple target DNAs of distinct sequence in a single reaction, which is what appellants allegedly claim. The relevance of appellants' assertion (brief, page 11, lines 19 and 20) that the present invention "provides" that primers which bind to more than one sequence can be used is questioned since such multiple binding is not claimed. Even if such multiple binding were explicitly claimed, it is believed that multiple binding would be inherent with primers to any set of related genes, such as immunoglobulin genes.

Appellants argue (Brief, page 12) that without the idea of cloning a repertoire of variable domain sequences there was no motivation for anyone to look for sequences which would enable repertoire cloning. Firstly, as noted supra, appellants are not specifically claiming the use of primers to conserved sequences such that an individual primer hybridizes

to multiple variable domain sequences. Secondly, it is the examiner's position that analysis of DNA sequences for identifying conserved or consensus sequences was a well known and well established method at the time the invention was made. In fact, such analysis was used to identify and label regions of immunoglobulins based on the level of sequence conservation. It is also submitted that sequence analysis and comparison was known to be one of the primary purposes of making public a list of sequences such as Kabat et al. Thus, one of ordinary skill in the art of immunoglobulin genes would have known how to analyze the sequences of Kabat et al. and for what purposes. Finally, it is submitted that, combined with the other references, one of ordinary skill in the art would have known how, and would have been motivated, to devise primers for the PCR cloning of variable domain sequences using the sequence information of Kabat et al. The large number of variable domain sequences provided by Kabat et al. would clearly have made it possible to clone a "repertoire" of variable domain sequences. In this regard, it is again emphasized that appellants are not claiming specific primers which would hybridize to and amplify multiple variable domain sequences of distinct sequence.

Appellants argue that impermissible hindsight has been applied in the instant rejection. Specifically, appellants take issue (Brief, page 15) with the examiner's assertion that one of ordinary skill in the art would have recognized that the general teachings of Mullis et al. and Herzog et al. could be applied to the cloning of variable domain sequences. Firstly, it is submitted that Mullis et al. and, to a lesser extent, Herzog et al. are explicit in the generic nature and wide applicability of their methods. Secondly, it is submitted that myriad genetic engineering techniques for the manipulation of DNA were known to the ordinary artisan at

the time the invention was made and that one of the central principles of such manipulations, also well known at the time the invention was made, was that DNA inherently possesses a set of common properties and utilities which make most individual DNA molecules interchangeable in most methods of DNA manipulation. Thus, for example, it would have been an article of faith, at the time the invention was made, that two DNA strands with complementary sequences would hybridize under predictable conditions. Indeed, Mullis et al. relies upon such interchangeability and common properties of DNA in their explicitly generic disclosure. Thirdly, it has not been established that the instantly claimed target sequences (variable domain sequences) have any properties that would suggest that they would not have been operable in the methods of Mullis et al., Herzog et al. or Skerra et al., when using primers derived from the sequences of Kabat et al.

Appellants again argue (Brief, page 15, bottom) that Mullis et al. and Herzog et al. fail to teach the use of primers which can hybridize to more than one different sequence of interest and also teach only primers which exactly match a target sequence. This argument has been answered more fully supra. Briefly, it is the examiner's position that 1) appellants are not claiming the use of primers which each bind more than one different sequence of interest, and 2) that Mullis et al. do teach the use of primers which do not exactly match a target sequence. In this regard, the examiner notes that Mullis et al. state (column 6, lines 56 to column 7, line 3) that:

> [t]he primers herein are selected to be "substantially" complementary to the different strands of each specific sequence to be amplified. This means that the primers must be

sufficiently complementary to hybridize with their respective strands. Therefore, the primer sequence need not reflect the exact sequence of the template.

Appellants assert (Brief, page 16) that there is nothing in any of the citations which suggests what to do if confronted with a very large number of different sequences and that it would be "ridiculous" to apply the one-gene-at-a-time approach allegedly taught by Mullis et al. to the cloning of a repertoire of variable domain sequences. Appellants are apparently relying here on their incorrect (as noted supra) allegation that the instantly invention claims the use of primers which bind to more than one variable domain sequence. Firstly, it is submitted that the examiner has provided teachings, a sufficient motivation to combine those teachings, and has established that one of ordinary skill in the art would have reasonably expected success at cloning a repertoire of variable domain sequences using the combined teachings. There is no requirement to provide teachings for limitations which are not claimed. Secondly, as noted supra, the instantly claimed method, insofar as it reads on cloning multiple target DNAs of distinct sequence, makes use of primers in the same way that Herzog et al. (and Mullis et al.) do. Specifically, primers which hybridize to a given target sequence will amplify that target sequence. Quoting from claim 33, appellants claim the use of forward and back primers with "the forward primer being specific for a sequence at or adjacent the 3' end of the sense strand of each the target sequences, the back primer being specific for a sequence at or adjacent the 3' end of the antisense strand of each of the target sequences." It is submitted that a primer "specific for a sequence" reads on the primers taught by Mullis et al. and Herzog et al. Appellants are not claiming the use of any primers with properties unobvious over those of the prior art. Finally, even if it were true that Mullis et al. teach an

embodiment of a method which would be "ridiculous" to apply to the cloning of variable domain sequences, the examiner is not obligated to apply the disclosure of such a "ridiculous" embodiment in a rejection (so long as such teaching did not impeach other teachings of the reference). In this regard it is noted that Mullis et al. disclose a wide variety of embodiments of PCR cloning of desired DNA sequences. It is further noted that the numerous variable domain sequences taught by Kabat et al. were obtained using such allegedly "ridiculous" approaches.

Appellants argue (Brief, page 16, middle) that Kabat et al. do not teach or suggest that there is sequence conservation such as to allow primers to be made and used in the cloning of immunoglobulin variable domain gene repertoires and that at most, Kabat et al. provide a short cut to cloning the genes disclosed therein. Firstly, as noted supra, appellants are not specifically claiming the use of primers to conserved sequences such that an individual primer hybridizes to multiple variable domain sequences. Secondly, it is the examiner's position that analysis of DNA sequences for identifying conserved or consensus sequences was a well known and well established method at the time the invention was made (see discussion supra). Finally, it is noted that Kabat et al. disclose a repertoire of immunoglobulin variable domain sequences from which it would be routine to devise primers which would be capable of amplifying at least one repertoire (i.e. the repertoire disclosed by Kabat et al.) of variable domain sequences. Since appellants do not limit the nature of the primers claimed to exclude the cloning of the sequences within the repertoire disclosed by Kabat et al., it is submitted that the method and the primers used therein are taught by the cited references.

Appellants also cite Larrick et al. (Brief, page 16, bottom and page 17) as teaching the state of the art prior to the instant invention. The examiner agrees that Larrick et al. do not teach the instant method of cloning immunoglobulin variable domains. In this regard it is noted that Larrick et al. has not been applied in the instant rejections. However, even though Larrick et al. teach a different method of cloning, the examiner is not obligated to apply the disclosure of such a "ridiculous" embodiment in a rejection (so long as such teaching did not impeach other teachings of the reference). In concluding that because Larrick et al. fail to teach the claimed (superior) method, such a method was unobvious over the art at the time the invention was made, appellants appear to imply that all published references necessarily use the only, or best, known method to achieve a goal . Such logic is faulty because there is no evidence that references always use the best method available. In addition, because the specifics of every research project differ, there may be strong reasons (which might not appear in a reference) for avoiding an obvious method in favor of another even though the method chosen may appear to be a poorer choice. Thus, Larrick et al., by itself, does not establish that the instantly claimed method was unobvious at the time the invention was made.

Appellants argue (Brief, page 18) that Schoemaker et al. do not remedy the alleged deficiencies of Skerra et al., Mullis et al., Herzog et al. and Kabat et al. The examiner agrees that Schoemaker et al. fails to teach some aspects of the invention. However, it is submitted that, as detailed supra, Skerra et al., Mullis et al., Herzog et al. and Kabat et al. together do teach every claimed aspect of appellants' invention except the expression of heterochain antibodies, for which teaching alone Schoemaker et al. is cited.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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